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Person signing the certificate:
Jay Akhave
Signature _____ *Date* 9.14.04

13 September, 2004

Commissioner for Patents
P O Box 1450
Alexandria
VA 22313-1450

Sub: Certified Foreign Priority Document on U.S. Application 10/676,914

Dear Sir:

This is a submission of certified priority documents for the following U.S. Patent application.

U S Patent Application No.	10/676,914
Filing Date	10/01/2003
Title	Process for preparing Cefdinir
First named Inventor	Ramesh Dandala
Art Unit	1614
Attorney Docket No.	2003-017
Filing Status	Filed awaiting First office Action

Sincerely,

Jay Akhave
845 Pomello Dr
Claremont CA 91711
909 625 3492
US Patent Agent No 50,016

Encl: Certified Copy of Indian Application No. 441/MAS/2003

THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copy of Application, Complete Specification & Abstract of the extract of Patent Application No.441/MAS/2003, dated 02/06/2003 by Aurobindo Pharma Limited having its registered office at Plot No.2, Maitrivihar Complex, Ameerpet, Hyderabad – 500 038, Andhra Pradesh, India.

.....

.....In witness thereof

I have hereunto set my hand

Dated this the 24th day of June 2004

M. S. V

(M.S. VENKATARAMAN)
ASSISTANT CONTROLLER OF PATENTS & DESIGNS

PA[illegible]NT [illegible]FICE BRANCH
GO[illegible]RN[illegible]NT OF INDIA
Gur[illegible] Com[illegible]ex, 6th Floor, Annex.II
No.[illegible], A[illegible] Salai, Teynampet,Chennai – 600 018

CERTIFIED COPY OF PRIORITY DOCUMENT

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441/MAS/03
2.6.03

ORIGINAL

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)
APPLICATION FOR GRANT OF A PATENT OFFICE
[See section 5(2), 7/54 and 135]

1. We

AUROBINDO PHARMA LIMITED
PLOT NO. 2, MAITRIVIHAR COMPLEX (Regd. Office)
AMEERPET
ANDHRA PRADESH
HYDERABAD – 500 038.
INDIA
(An Indian Organization)

2. Hereby declare: -

(a) That we are in possession of an invention titled: -

"A ~~NOVEL INTERMEDIATE, 2-MERCAPTOBENZOTHIAZOLYL- (Z)-2-(2-AMINO-4-THIAZOLYL) 2-ACETYLOXYIMINOACETATE AND ITS USE TO PREPARE CEFDINIR~~." NEW PROCESS FOR PREPARING CEFDINIR

(c) That the Complete Specification relating to this invention is filed with this application.

(d) That there is no lawful ground of objection to grant of a Patent to us.

3. Further declare that the inventor(s) for the said invention is: -

(a) **RAMESH DANDALA**

(b) **V.V.PRASADA RAO KORRAPATI**

(c) **MEENAKSHISUNDERAM SIVAKUMARAN**

C/o. AUROBINDO PHARMA LIMITED
PLOT NO. 2, MAITRIVIHAR COMPLEX (Regd. Office)
AMEERPET
ANDHRA PRADESH
HYDERABAD – 500 038.
INDIA

(a) to (c) : **CITIZENS OF INDIA**

4. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows:-

(a) NIL

(b) NONE

5. We state that the said invention is an improvement in or modification of the particulars of which are as follows and of which we are the Applicant/Patentee:

(a) NIL

(b) NONE

6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application be deemed to have been filed on .... under section 16 of the Act:

NONE

7. That we are the assignee or legal representative of the true and first Inventors.

8. That our addresses for service in India is as follows:

AUROBINDO PHARMA LIMITED
Plot No. 2, Maitrivihar Complex,
Ameerpet
Andhra Pradesh
Hyderabad - 500 038
India
Phone No.: 91-40-23741083
Fax No. : 91-40-23741080, 23740591

9. Following declaration was given by the inventor(s) or applicant(s) in the convention country:-

NONE

We the true and first inventors for the invention, declare that the applicant(s) herein are our assignee

(a) RAMESH DANDALA

(b) V.V.PRASADA RAO KARRAPATI

(c) MEENAKSHISUNDERAM SIVAKUMARAN

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Following are the attachment with the application: -

(a) Complete Specification (3 copies).

(b) Drawings (Nil)

(c) Priority document(s)

(d) Fee Rs. 5000/- in Bank Draft bearing No..... dated 1-06-03 on State Bank of Hyderabad.

We request that a Patent may be granted to us for the said invention.

Dated this 30th day of May 2003.

AUROBINDO PHARMA LTD. INDIA HYDERABAD

.....

(Dr. M. SIVAKUMARAN)
DIRECTOR

TO
THE CONTROLLER OF PATENTS,
THE PATENT OFFICE,
CHENNAI

Form-2

THE PATENT ACT, 1970

COMPLETE

SPECIFICATION

(SECTION 10)

TITLE

"A NEW PROCESS FOR PREPARING CEFDINIR"

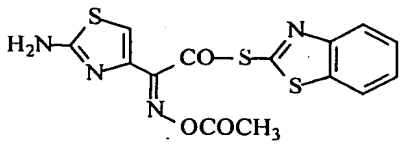
APPLICANT

AUROBINDO PHARMA LIMITED
HAVING REGISTERED OFFICE AT
PLOT NO. 2, MAITRI VIHAR COMPLEX,
AMEERPET, HYDERABAD – 500 038,
ANDHRA PRADESH, INDIA,
AN INDIAN ORGANIZATION

The following specification particularly describes and ascertains the nature of this invention and the manner in which the same is to be performed.

FIELD OF THE INVENTION

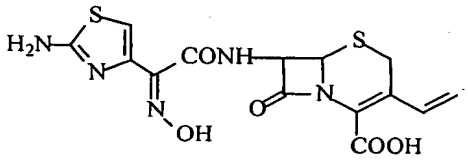
The present invention relates to a process for the preparation of Cefdinir by using intermediate, 2-mercapto-benzothiazolyl(*Z*)-2-(2-amino-4-thiazolyl)-2-acetyloxyiminoacetate of Formula I,



Formula I

BACKGROUND OF THE INVENTION

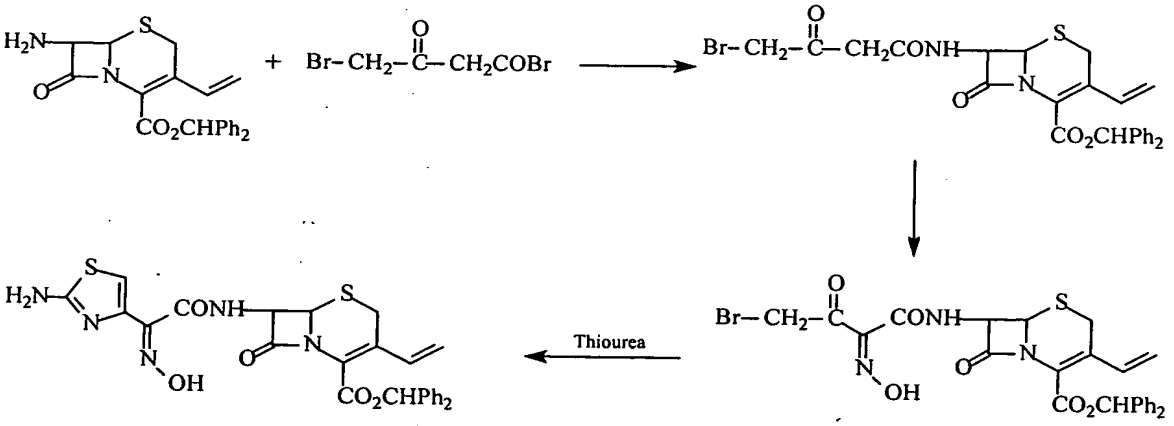
Cefdinir of Formula II is a oral, semi-synthetic cephalosporin antibiotic characterized by having a broad spectrum of antibacterial activity particularly against *Staphylococci* and *Streptococci* and a high stability against various β-lactamases. It further exhibits an enhanced activity against gram positive bacteria as well and is chemically known as 7β-[(Z)-2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid.

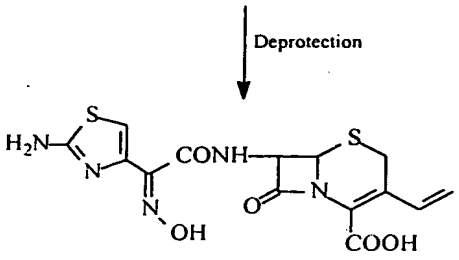


Formula II

Several synthetic methods are known in literature for preparation of cefdinir. For example, US Patent 4,559,334 describes a synthetic method starting from benzhydryl 7-amino-3-vinyl-3-cephem-4-carboxylate which is reacted with 4-bromoacetoacetyl bromide, the resulting product is nitrosated to oxime and cyclized to obtain protected cefdinir. Deprotection yielded cefdinir (Refer Scheme-1). However, this synthetic method suffers from several disadvantages such as use of not so easily available raw materials, low yielding steps and isolation involving chromatography and lyophilisation. Overall yield reported is 10-11%.

Scheme-1





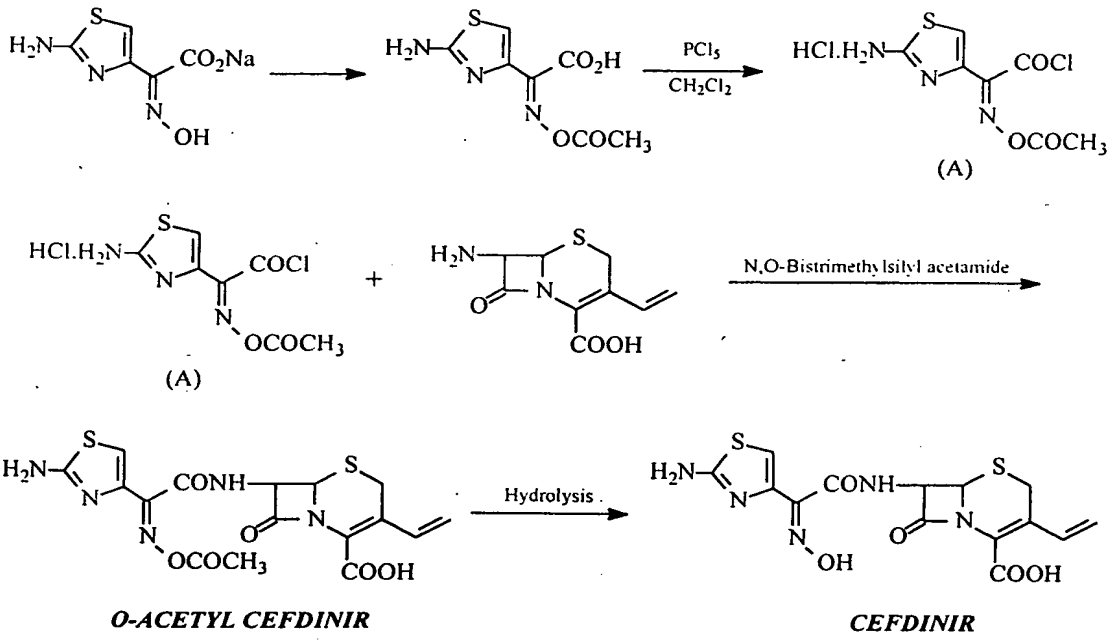
CEFDINIR

Ph: Phenyl

Spanish Patent ES 2 013 828 describes alternate route to prepare Cefdinir overcoming the difficulties in US Patent 4,559,334 (Refer Scheme-2).

Thus, (*Z*)-2-(2-amino-4-thiazolyl)-2-acetyloxyiminoacetic acid was prepared and converted into corresponding acid chloride hydrochloride (A) via reaction with phosphorus pentachloride and condensed with 7-amino-3-vinyl-3-cephem-4-carboxylic acid to yield O-acetyl Cefdinir which was deprotected to yield Cefdinir.

Scheme-2

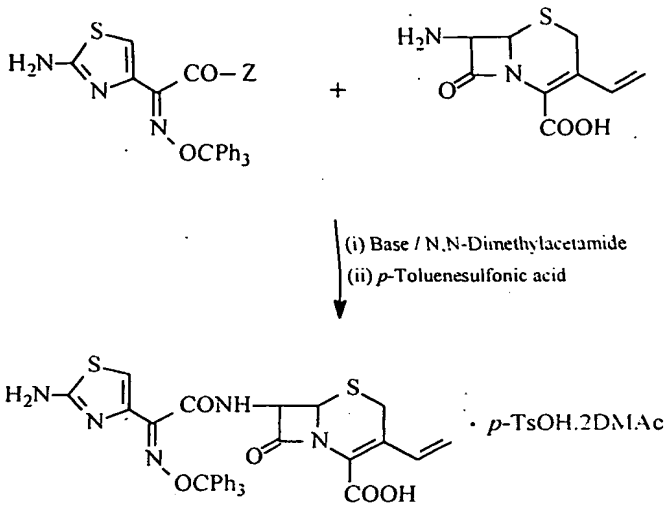


O-ACETYL CEFDINIR ***CEFDINIR***

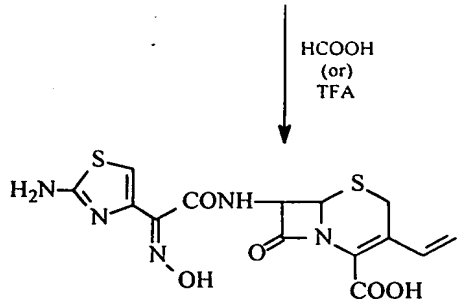
However, in our hands the preparation of (*Z*)-2-(2-amino-4-thiazolyl)-2-acetyloxyiminoacetylchloride hydrochloride did not prove to be consistent, possibly due to nature of side chain sodium salt and a lot of impurity formation was observed. Moreover this reaction resulted in incomplete conversion and formation of anti-isomer was also observed. Further, this process requires very low temperature leading to additional burden on equipment.

US Patent 6,093,814 describes a process wherein tritylated cefdinir is prepared and isolated as O-trityl cefdinir.*p*-toluenesulfonic acid.2*N*,*N*-dimethylacetamide solvate and further converted into cefdinir either by treatment with formic acid or trifluoroacetic acid (Refer Scheme-3). The disadvantages of this process are use of ethers to isolate O-trityl cefdinir.*p*-toluenesulfonic acid.2*N*,*N*-dimethylacetamide solvate which greatly enhances danger of fire hazard on a commercial scale and poor solvent recovery. Further, the specified yields could not be realized by us in detritylation step.

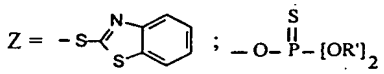
Scheme-3



O-TRITYL CEFDINIR



CEFDINIR



Ph = Phenyl

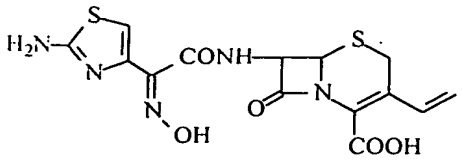
Detritylation to obtain cefdinir by using a perhalogenated acids has been described by Otsuka Chemical Company in EP 1 273 587 A1. However, this process also gave low yields and further handling and disposal of perhalogenated acids poses an industrial hazard.

Thus, it is evident that the intermediates described in the prior art to prepare Cefdinir include an acid chloride, a reactive thiophosphate, a reactive ester and the like. However, these

intermediates have some disadvantages such as low yields, expensive input raw materials and handling problem in commercial production. Hence, there is a need to use such acylating agent which is capable of transferring the 2-aminothiazolyl moiety to 7-amino-3-cephem compound in good yield without producing any side product and without requiring complicated protection / deprotection operations.

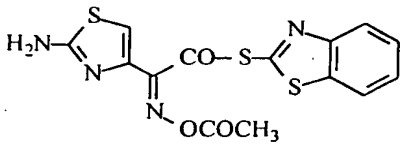
SUMMARY OF THE INVENTION

The present invention relates to a process for the preparation of Cefdinir of Formula II



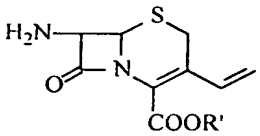
Formula II

by reacting O-acetyl thioester of Formula I



Formula I

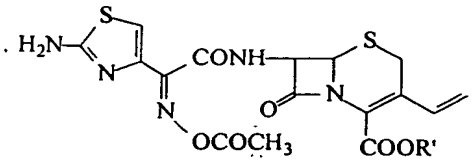
with the cephem compound of Formula III



Formula III

wherein R' = H, any carboxyl protecting group or silyl group

in the presence of base, in suitable solvent at a temperature of 10-25°C to prepare protected Cefdinir Formula IV



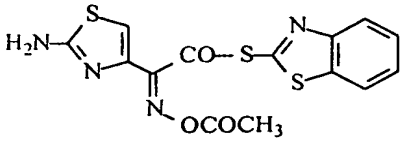
Formula IV

wherein R' = H, any carboxyl protecting group or silyl group

and conversion of the above protected cefdinir to Cefdinir by removal of protecting groups using conventional methods.

DETAILED DESCRIPTION OF THE INVENTION

The instant invention relates to an industrially advantageous process for the preparation of cefdinir, which involves the use of intermediate, 2-mercaptobenzothiazolyl (*Z*)-2-(2-amino-4-thiazolyl)-2-acetyloxyiminoacetate (O-acetyl thioester), of Formula I.



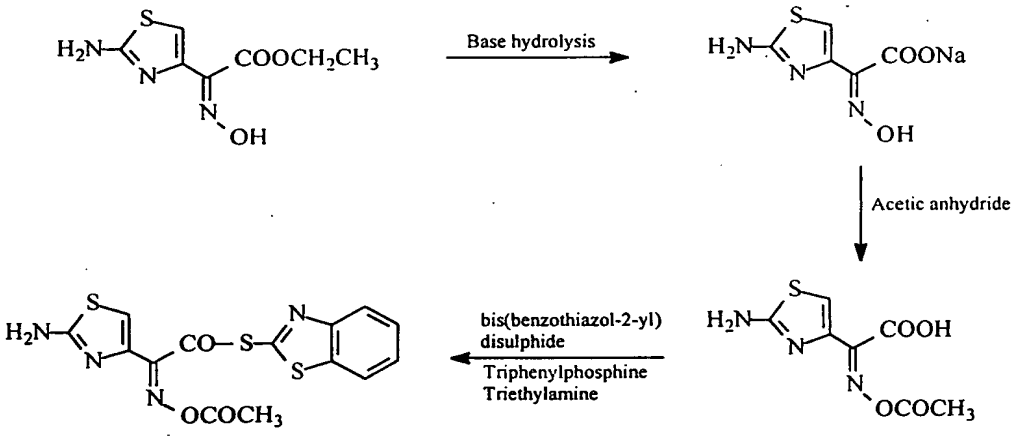
Formula I

2-Mercaptobenzothiazolyl (*Z*)-2-(2-amino-4-thiazolyl)-2-acetyloxyiminoacetate (O-acetyl thioester), of Formula I was reported in US Patent 4,888,429, but its use to prepare Cefdinir has never been reported and constitutes novelty.

Further, the present invention provides a new method for the preparation of intermediate, O-acetyl thioester and its valuable use in the preparation of pure cefdinir.

The intermediate, O-acetyl thioester can be prepared by condensation of (Z)-2-(2-amino-4-thiazolyl)-2-acetyloxyiminoacetic acid with *bis*(benzothiazol-2-yl)disulphide, in the presence of triphenylphosphine and a base in a suitable solvent at 0-35°C (Refer Scheme-4).

Scheme-4



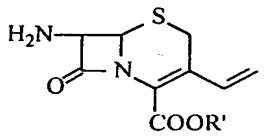
Formula I

Suitable solvents can be selected from a group of methylene dichloride, chloroform tetrahydrofuran, acetonitrile or like and mixture thereof; but the most preferred ones are methylene dichloride and tetrahydrofuran.

Typically reaction can be conducted at a temperature range of about 0-35°C, but preferably at 10-30°C. The bases, which can be used, are tertiary organic bases such as tributylamine, triethylamine or like, but preferably triethylamine is used. After completion of reaction, the product which precipitates out spontaneously from the reaction mass is isolated by filtration.

(Z)-2-(2-amino-4-thiazolyl)-2-acetyloxyiminoacetic acid for the preparation of O-acetyl thioester is prepared by known process as described in ES 2 013 828. The commercially available ethyl (Z)-2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetate is treated with aqueous sodium hydroxide in ethanol to yield corresponding sodium salt. The resulting sodium salt is acylated with acetic anhydride maintaining pH between 7.0 to 8.0 using potassium carbonate to yield (Z)-2-(2-amino-4-thiazolyl)-2-acetyloxyiminoacetic acid (acylated acid). We have observed that variation in pH results in the formation of diacylated product. The acylated acid typically has ~14% of moisture content. It is preferable to use dehydrated acylated acid for the preparation of O-acetylthioester. Use of dehydrated acylated acid avoids the excess consumption of reagents and minimizes exothermicity. Dehydration can be carried out in any suitable solvent like methanol, ethanol, acetone etc., but most preferably dehydration is effected in acetone to obtain acylated acid having moisture content ≤ 0.5%. This dehydrated acylated acid can preferably be used in preparation of O-acetyl thioester as discussed above.

Thereafter, the O-acetyl thioester of Formula I is reacted with cephem of Formula III in the presence of a base, in any suitable solvent at a temperature range of 10-25°C but preferably at 20-25°C.



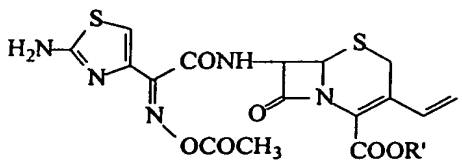
Formula III

R' in compound of Formula III may be any carboxyl protecting group. The term carboxyl protecting group as used herein refers to a protecting group which is conventionally used in cephalosporin based compounds and exemplary protecting group includes silyl group; alkyl esters such as methyl and *t*-butyl; alkoxylkyl such as methoxymethyl; alkyl thioalkyl esters such as methyl, thiomethyl; haloalkyl esters such as 2,2,2-trichloroethyl and aralkyl ester, such as benzyl, *p*-methoxybenzyl, *p*-nitrobenzyl, diphenylmethyl; wherein *p*-methoxybenzyl, *p*-nitrobenzyl and diphenylmethyl are preferred.

The suitable solvent can be selected from a group of water, tetrahydrofuran, methylene dichloride or mixture thereof, but preferably solvent is aqueous tetrahydrofuran.

The base can be selected from inorganic bases such as sodium bicarbonate, sodium carbonate or organic bases such as alkylamines preferably tertiary alkylamines like triethylamine, diisopropylethylamine, tributylamine etc. Particularly preferred base is triethylamine.

The progress of reaction is monitored by HPLC till cephem of Formula III is less than 1%. Thereafter reaction mass is diluted with any suitable solvent and protected cefdinir of Formula IV



Formula IV

wherein R' = H, any carboxyl protecting group or silyl group

is extracted with water. Protected cefdinir of Formula IV is optionally isolated and can also be deprotected *in situ* to obtain Cefdinir.

The major advantages realized in the present inventions are preparation of O-acetyl thioester which offers the best feature of acylation to introduce side chain on compound of Formula III and preparation of O-acetyl cefdinir in good yields and high purity. Such a methodology overcomes the difficulties experienced in the prior art such as low yields, poor quality and handling problem in commercial production.

Hence the present invention for the preparation of cefdinir is suitable for plant scale production and Cefdinir is obtained in high yield and high quality consistently.

Further the following examples will illustrate the preparation of O-acetyl thioester and cefdinir and are not to be construed as any limiting thereof:

Example 1

PREPARATION OF 2-MERCAPTOBENZOTHIAZOLYL (Z)-2-(2-AMINO-4-THIAZOLYL)-2-ACETYLOXYIMINOACETATE *(O-ACETYL THIOESTER)*

55 g of (Z)-2-(2-amino-4-thiazolyl)-2-acetyloxyiminoacetic acid (0.240 mol, moisture content: 0.49% w/w) was added to 825 ml of methylene dichloride at 20°C. Cooled the reaction mass to 15-20°C. To this mixture, 111.6 g of *bis*(benzothiazol-2-yl)disulphide (0.336 mol) and 91.2 g of triphenylphospine (0.348 mol) were added at 10-15°C. To this reaction mixture, 34 g of triethylamine (0.336 mol) was added at 10-15°C during a period of 5-10 min. Maintained the reaction mass temperature at 10-30°C till starting material is ≤ 2% by qualitative HPLC analysis (~1 h). Cooled the reaction mixture to 5-10°C and filtered the precipitated product. Washed with 300 ml of methylene dichloride at 5-10°C. Dried the product at 35-40°C under reduced pressure till LOD ≤1% w/w. 74 g of product was isolated which showed greater than 94% purity by HPLC.

Melting point: 143-145°C.

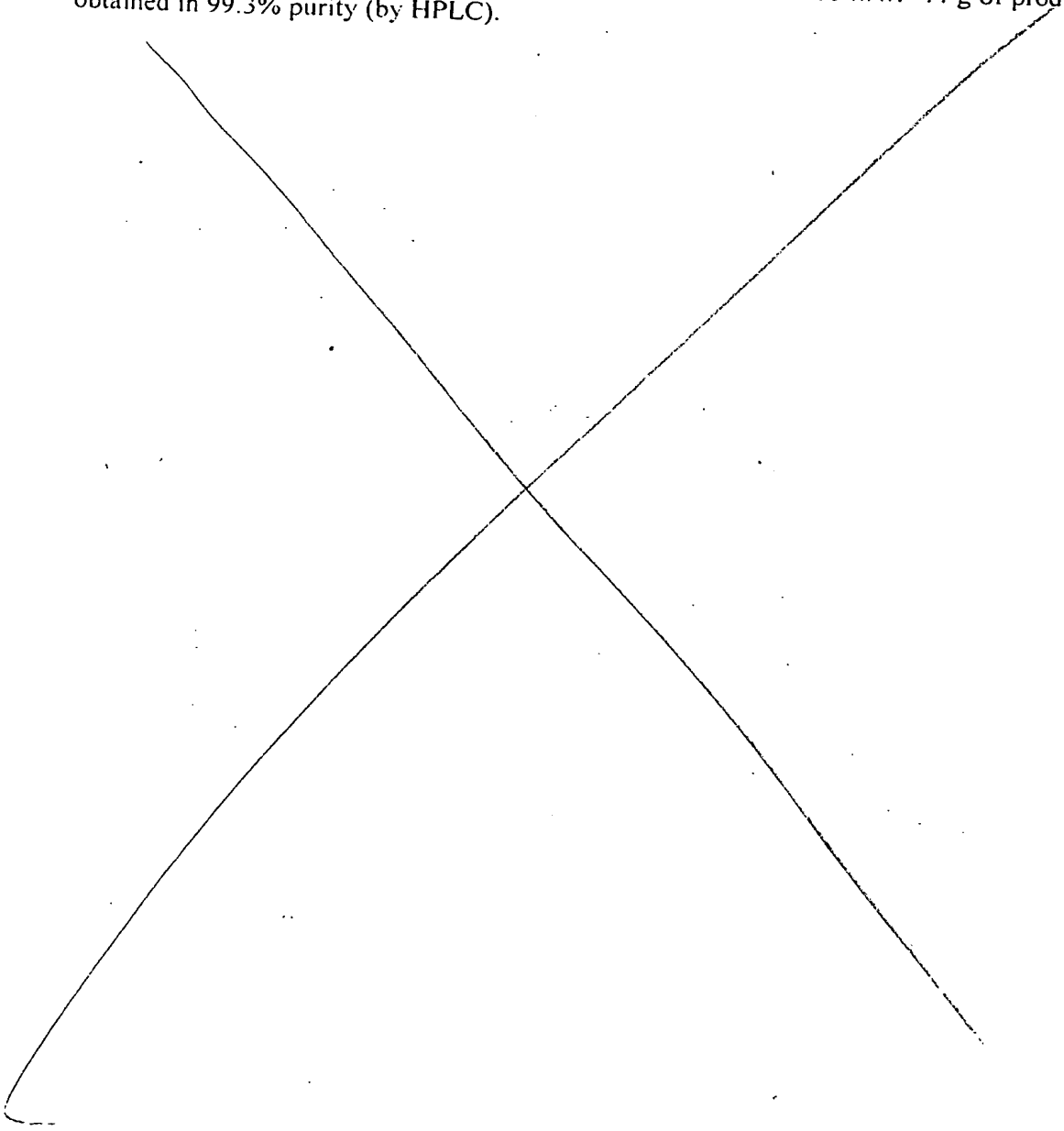
INFRARED ABSORPTION SPECTRUM (IR) *(Cm^{-1}, KBr)*	:	*3446, 3101, 1777, 1645, 1618*
^{1}H-NMR in DMSO-d_6	:	*δ(ppm); 2.23 (s, 3H); 7.38(s,1H); 7.52(s, 2H); 7.55-7.65 (m, 2H); 8.09 (d, 1H, J=9 Hz), 8.23 (d, 1H, J=9 Hz).*

Example 2

PREPARATION OF 7β-[(Z)-2-(2-AMINO-4-THIAZOLYL)-2-HYDROXYIMINO ACETAMIDO]-3-VINYL-3-CEPHEM-4-CARBOXYLIC ACID *(CEFDINIR)*

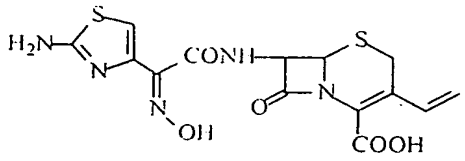
40 g of 7-amino-3-vinyl-3-cephem-4-carboxylic acid (AVNA, 0.177 mol) was added to 400 ml of tetrahydrofuran under nitrogen atmosphere followed by 78 g of O-acetyl thioester

(0.206 mol, prepared in Example 1) and 200 ml of water with stirring. Cooled the reaction mass to 15-20°C. To this reaction mixture, 20 g of triethylamine was added slowly at pH ~8.5. Stirring was continued and progress of the reaction was monitored by qualitative HPLC till AVNA was less than 1%. At this stage 400 ml of methylene dichloride was added and stirred for further 15 min at 20-25°C. 200 ml of water was added and stirred the reaction mass for 15 min at 20-25°C. Separated the layers and to the aqueous layer, 20% w/v aqueous potassium carbonate solution was added and maintained pH at 8.1-8.2 at 20-25°C. Thereafter, 26.4 g of ammonium chloride was added in one lot at 20-25°C and continued maintaining the pH between 8.0 to 8.2 by addition of 20% w/v aqueous potassium carbonate solution. The progress of reaction was monitored by qualitative HPLC till O-acetyl cefdinir is less than 0.5%. Adjusted the pH of reaction mass to 2.4-2.5 with conc. sulfuric acid maintaining temperature between 35° to 40°C. The precipitated product was filtered and dried at 40-45°C under reduced pressure till moisture content was ≤ 2% w/w. 44 g of product was obtained in 99.3% purity (by HPLC).



WE CLAIM:

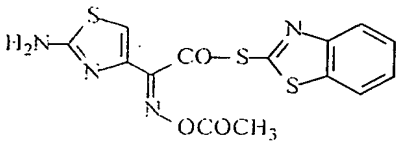
1. A process for preparing Cefdinir of Formula II



Formula II

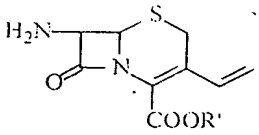
wherein R' = H, any carboxyl protecting group or silyl group

which comprises
- reacting O-acetyl thioester of Formula I



Formula I

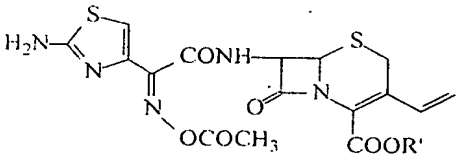
with a Compound of Formula III



Formula III

wherein R' = H, any carboxyl protecting group or silyl group

in the presence of a base such as triethylamine, diisopropylethylamine, tributylamine, sodium carbonate, sodium bicarbonate, in suitable solvent like water, tetrahydrofuran, methylene dichloride and mixture thereof, at a temperature of 15-20°C, to obtain a compound of Formula IV,



Formula IV

wherein R' = H, any carboxyl protecting group or silyl group

- converting compound of formula IV to cefdinir by removal of protecting group(s) using a base and
- isolating the cefdinir formed, by the pH adjustment with acid such as sulfuric acid.

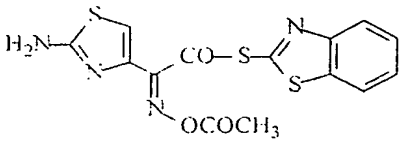
2. The process according to claim 1 wherein the preferred base used is triethylamine.

3. The process according to claim 1 wherein preferred solvent used is a mixture of tetrahydrofuran and water.

4. The process according to claim 1 wherein the said reacting step is conducted at a temperature between 10-25°C and preferably at 15-20°C.

5. The process according to Claim 1 wherein the carboxyl protecting group is selected from *p*-methoxybenzyl, *p*-nitrobenzyl and diphenylmethyl.

6. The process according to claim 1, wherein O-acetyl thioester of Formula I



Formula I

is prepared by the process which comprises

- condensation of (Z)-2-(2-amino-4-thiazolyl)-2-acetyloxyiminoacetic acid with bis(benzothiazol-2-yl)disulphide in the presence of triphenylphosphine, a base such as tributylamine and triethylamine, in a suitable solvent like methylene dichloride, chloroform, tetrahydrofuran, acetonitrile and mixture thereof, at a temperature of 0-35°C.

7. The process according to claim 6 wherein the preferred base used is triethylamine.

8. The process according to claim 6 wherein the preferred solvent used is methylene dichloride.

9. The process according to claim 6 wherein the said reacting step is conducted at a temperature between 0-35°C and preferably at 10-20°C.

Dated this the 30th day of May 2003

AUROBINDO PHARMA LIMITED,

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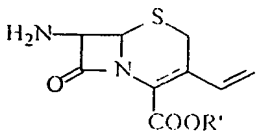
DIRECTOR.

ABSTRACT

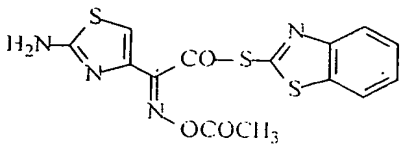
The present invention relates to a process for the preparation of Cefdinir by acylating the cephem compound of formula III



Formula III

wherein R' = H, any carboxyl protecting group or silyl group

using intermediate, 2-mercapto-benzothiazolyl(Z)-2-(2-amino-4-thiazolyl)-2-acetyloxyiminoacetate of Formula I,



Formula I

followed by hydrolysis.